administering to said mammal an autoimmune-preventing effective amount of non-infectious *Coxiella burnetii* or one or more antigenic components therefrom.

15. (Thrice Amended) A therapeutic composition for use in prophylaxis or treatment of an insulin-dependent diabetes mellitus autoimmune disease in a mammal, said composition comprising non-infectious *Coxiella burnetii* or one or more antigenic components therefrom and one or more pharmaceutically acceptable carriers and/or diluents.

REMARKS

Favorable reconsideration of the instant application in view of the present amendments and the following comments is respectfully requested. Claims 1-4, 6-8, 15-17 and 19-21 are under examination in this application. Claims 1 and 15 have been amended in order to more clearly set forth one aspect of the instant invention. Support for the above amendments can be found throughout the specification, for example, at page 20 through 25 (Examples 1-5), at page 17, lines 26-29, at page 18, lines 7-9, at page 5, lines 10-11, at page 6, line 1, and elsewhere. It should be noted that the above amendments are not to be construed as acquiescence with regard to the Action's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application.

Rejection Under 35 U.S.C. § 112, first paragraph

The Action maintains the ground for rejection of claims 1-4, 6-8, 15-17 and 19-21 under 35 U.S.C. § 112, first paragraph, presented in paragraph 12 of the Office Action mailed March 21, 2001, alleging that the specification does not enable the full scope of subject matter as claimed. In particular, the Action alleges that the recited subject matter as currently claimed, "autoimmune disease" and "one or more antigenic components", are not within the scope of the instant specification. More specifically, the Action alleges that the Declaration provided by William Butler Cowden, Kevin John Lafferty and Lawrence Scott Gazda (hereinafter referred to

as the Cowden Declaration) provides further evidence that the entire scope of the above-mentioned claims is not enabled.

Applicants respectfully disagree and traverse this ground of rejection. Applicants submit that, as set forth by the instant specification, the full scope of the current claims is readily enabled by the use of non-infectious *Coxiella burnetii* (*C. burnetii*) or active components thereof in the prevention and/or treatment of an autoimmune disease in a mammal, for example insulin-dependent diabetes mellitus (IDDM). In pertinent part, Applicants strongly disagree with the Action's interpretation of the Cowden Declaration. The facts presented by the Cowden Declaration are, in pertinent part, consistent with the instant specification and the subject matter as claimed, in that, components of *C. burnetii* contained in one extracted fraction as opposed to another fraction are shown to have activity in preventing, inhibiting, delaying the onset or otherwise ameliorating the effects of an autoimmune disease (*e.g.*, IDDM) in a mammal. It is submitted, that the Cowden Declaration merely provides demonstrative evidence which further confirms that the instant specification, as it was originally filed, teaches how, and thereby enables, one of ordinary skill in the art at the time the instant application was filed, to identify preparations of non-infectious *C. brunetii* or antigenic components derived therefrom that function in preventing, inhibiting, delaying onset of or ameliorating the effects of (*i.e.*, the prophylaxis and/or treatment of) an autoimmune disease such as, for example, IDDM. In this regard, the instant specification teaches, and the Cowden Declaration further confirms, that preparations of non-infectious *C. brunetii* as well as some but not other components derived therefrom retain activity, thereby providing a method for preventing, inhibiting, delaying onset of or ameliorating the effects of an autoimmune disease in a mammal, said method comprising administering to said mammal an autoimmune-preventing effective amount of non-infectious *Coxiella brunetii* or one or more components therefrom.

Further, Applicants submit that according to the instant specification, a component (*e.g.*, a part or minimum number of parts required to produce the activity of the whole) of *C. brunetii* may be used to practice the full scope of the claimed method. For example, at page 17, line 26-29, the instant specification teaches that the principal active component may be prepared for convenient and effective administration in an effective amount, which may be in a dosage unit where the principal active component from about 0.1ug to about

200mg. The specification, as originally filed, also discloses, at page 18, line 7-9, that active components of the present invention may be administered alone or in combination with other therapeutic molecules. In this context, the Cowden Declaration further confirms that active components of *C. burnetii*, as disclosed by the specification in its original form, may be used for preventing, inhibiting, delaying onset of or otherwise ameliorating the effects of an autoimmune disease, for example, IDDM. In particular, the Cowden Declaration demonstrates, using common procedures known to those of ordinary skill, that a delipidated extract of *C. Burnetii* containing one or more components of *C. burnetii* (*i.e.*, an extracted fraction containing active components that are in-sum less than the whole) can be distinguished from *C. burnetii* components contained in, comparatively speaking, an inactive fraction. In a similar manner, active components of *C. burnetii* may be distinguished from inactive components by way of DMSO extraction. Applicants submit, therefore, that the demonstrated use of active components in the widely accepted IDDM model system, the NOD mouse, using equally well accepted procedures to prepare fractions containing such active components, clearly sets forth and teaches how to practice the instant invention, without undue experimentation, to the full scope as currently claimed, as would be appreciated by those of ordinary skill in the art at the time the instant application was filed.

The ability for one of ordinary skill to practice the full scope of the claimed method for preventing, inhibiting and delaying the onset of IDDM with a non-infectious form of *C. burnetii* is further evidenced by the instant specification in Examples 1-5, using the well accepted NOD mouse model system for IDDM. In Example 1-3, non-infectious *C. brunetii* is used to ameliorate IDDM which spontaneously develops in the NOD mouse model system. The ability to ameliorate the effects of IDDM in such a model system is demonstrated even further, for example, by the prevention of diabetes in transplanted as well as non-transplanted insulin producing cells. In Example 4, the development of diabetes is prevented in the transplanted islet cells and ameliorated in the non-transplanted islet cells. In this case, the recipient of the donor cells was determined to be diabetic for at least 3 days and as long as 2 weeks prior to transplantation. Thus, the instant specification clearly teaches that non-infectious preparations of *C. burnetii* as well as active components derived therefrom may be identified and used for preventing, inhibiting, delaying onset of or otherwise ameliorating the effects of an autoimmune

disease in a mammal, said method comprising administering to said mammal an autoimmune-preventing effective amount of non-infectious *Coxiella burnetii* or one or more antigenic components therefrom. However, in order to advance prosecution of the instant application to allowance, and without acquiescing to the Action's ground for rejection and without prejudice to prosecution of similar subject matter in any related divisional, continuation or continuation-in-part, Applicants have amended claim 1 and 15 to specifically recite an insulin-dependent diabetes mellitus autoimmune disease, thereby further obviating the ground for this rejection. Support for such an amendment may be found in the examples and throughout the instant specification. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 15, 16, 20 and 21 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhang *et al.* (*Acta Virologica 38*:327-332, 1994), or Gajdosva *et al.* (*Acta Virologica 38*:339-344, 1994), each in view of Levy *et al.* (*Eur. J. Epidemiol. 5*:447-453, 1989, abstract) or Roue *et al.* (*Lancet 341*:1094-1095, 1993). More specifically the Action alleges that Levy *et al.* and Roue *et al.* teach the autoimmune nature of Q-fever and that Zhang *et al.* or Gajdosova *et al.* teach a composition comprising components of *C. brunetii* that confer immunity against Q-fever, a disease being autoimmune in nature.

Applicants disagree with the Action's interpretation of the cited art and respectfully traverse the ground for this rejection. First as discussed by Zhang *et al.* and Gajdosova *et al.*, infection with *C. brunetii* results in an indication referred to as Q-fever. Zhang *et al.* and Gajdosova *et al.* also demonstrate that a *C. brunetii* infection may be prevented by immunization with an outer membrane component of *C. brunetii*. However, autoimmunity is neither taught or suggested by either Zhang *et al.* or Gajdosova *et al.* Further, the disclosures of Zhang *et al.* and Gajdosova *et al.* provide no motivation for one of ordinary skill in the art to even consider the use of non-infectious *C. brunetii* or active components derived thereof in the prevention, inhibition, delaying onset of or otherwise ameliorating the effects of an autoimmune disease in a mammal. Rather, both Zhang *et al.* and Gajdosova *et al.*, merely disclose that immunization with an outer membrane component of *C. burnetii* may be used to prevent *C.*

brunetii infection, as would be expected by one of ordinary skill in the relevant art. However, in clear contrast, the instant specification does not teach immunity to *C. brunetii* infection, but instead teaches and claims the surprising discovery of being able to use such components in methods for preventing, inhibiting, delaying onset of or otherwise ameliorating an apparently unrelated autoimmune disease in a mammal, for example IDDM. It is readily appreciated by those of ordinary skill in the art at the time the instant application was filed that the whole infectious agent or components of an infectious agent (*e.g.*, a microorganism) may be used to immunize a mammal against infection by that infectious agent. However, according to the teachings of the instant specification and as recited in the claims, what is extremely surprising and unexpected is that a non-infectious agent, or one or more active component thereof, can be used to prevent, inhibit, delay onset of or ameliorate the effects of an unrelated disease, for example, IDDM.

Further, neither Levy *et al.* nor Roue *et al.*, alone or in any combination, remedy the deficiencies of either Zhang *et al.* or Gajdosova *et al.* For example, Roue *et al.* address the psychiatric condition of a patient suspected of being infected with *C. brunetii*, a consequence of which appears to involve the central nervous system and neurological dysfunction. However, Gajdosova *et al.* does not teach, suggest or motivate one of ordinary skill in the art to the notion of autoimmunity or an autoimmune disease. Further still, Levy *et al.* merely disclose that the incidence (6 patients out of 104) of patients with an autoimmune disorder (apparently preexisting and not caused by *C. brunetii* infection) in a subpopulation of patients presenting symptomatic conditions associated with a *C. brunetii* infection could explain the manifestation of acute Q-fever, like resistance to antibiotic therapy. The disclosure of Levy *et al.* does not, in any way, state that Q-fever causes autoimmunity, but instead that the complications of autoimmune conditions affect the severity and ability of conventional therapies in the treatment of *C brunetii* infection. Applicants point out that Levy *et al.* at line 9-10, clearly state that no correlation between Q-fever and smooth muscle antibodies titers and kinetics were found (the marker of immunity used by Levy *et al.*). Levy *et al.*, in plain fact, do not teach or suggest that Q-fever actually results in the generation of a consequent autoimmune marker and certainly do not teach or suggest the claimed methods for the prophylaxis and/or treatment of an autoimmune disease of the instant application.

Thus, when viewed together, Zhang *et al.* or Gajdosva *et al.*, in further view of Levy *et al.* or Roue *et al.* do not teach, suggest or motivate one of ordinary skill in the art at the time the was filed to consider the instant invention as claimed, the use of non-infectious *C. brunetii* or components thereof to prevent, inhibit, delay onset of or ameliorate the effects of an autoimmune disease in a mammal, said method comprising administering to said mammal an autoimmune-preventing effective amount of non-infectious *Coxella brunetii* or one or more antigenic components therefrom, which by way of example and not in limitation may be IDDM. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-4, 6-8, 15-17 and 19-21 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim subject matter which Applicants regard as the invention. In particular, the Action alleges that the difference between recitation of the terms preventing, inhibiting, delaying onset of or otherwise ameliorating in claims 1 and 15 is unclear.

Applicants respectfully traverse the ground for this rejection. Applicants note, that the subtle differences between the recited terms would be appreciated by one of ordinary skill in the relevant art. For example, by way of generally accepted working definitions the term prevent is understood to mean to keep from happening; while inhibit means to restrict or hold back (but not necessarily to prevent); delay is causing something to be detained; and ameliorate means to improve an already existing condition. According to the instant application, non-infectious *C. brunetii* or one or more components thereof, may (i) be used to prevent spontaneous development of an autoimmune disease, for example, IDDM, or (ii) be used to inhibit development of, for example, autoimmunity to transplanted islet cells, or (iii) as a way to delay the development of an autoimmune disease that spontaneously develops or, (iv) to ameliorate (*i.e.*, a treatment for) an autoimmune disease that has already been detected. Thus, in the varying context of autoimmune disease conditions, and in some cases, the use of transplanted cells in the treatment of such disease conditions, all terms may be distinguished one from the other. According to the instant specification, non-infectious *C. brunetii* or one or more active

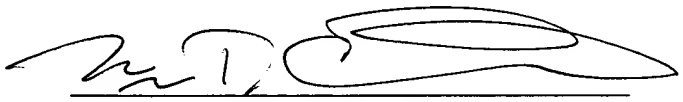
components derived therefrom is effective when used to prevent, and/or inhibit, and/or delay onset of, and/or ameliorate the effects of an autoimmune disease in a mammal, such as, IDDM. However, in order to advance prosecution of the instant application to allowance, and without acquiescing to the Action's ground for rejection and without prejudice to prosecution of similar subject matter in any related divisional, continuation or continuation-in-part, Applicants have amended claim 1 and 15 to recite prophylaxis or treatment of an insulin-dependent diabetes mellitus autoimmune disease, thereby further obviating the ground for this rejection. Support for such an amendment may be found at for example, page 5, line 10-11, and page 6, line 1, and throughout the instant specification. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1 and 15 have been amended as follows:

1. (Thrice Amended) A method for [preventing, inhibiting, delaying onset of or ameliorating the effects] a prophylaxis or treatment of an insulin-dependent diabetes mellitus autoimmune disease in a mammal, said method comprising administering to said mammal an autoimmune-preventing effective amount of non-infectious *Coxiella burnetii* or one or more antigenic components therefrom.

15. (Thrice Amended) A therapeutic composition for use in [preventing, inhibiting, delaying onset of or ameliorating the effects] a prophylaxis or treatment of an insulin-dependent diabetes mellitus autoimmune disease in a mammal, said composition comprising non-infectious *Coxiella burnetii* or one or more antigenic components therefrom and one or more pharmaceutically acceptable carriers and/or diluents.

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